Osteoarthritis and Cartilage 23 (2015) 2184–2190

Osteoarthritis and Cartilage

OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Brief Report

Knee joint subchondral bone structure alterations in active athletes: a cross-sectional case–control study

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ARTICLE INFO

Article history:
Received 3 March 2015
Accepted 7 July 2015

Keywords:
Athletes
Sports
Football
Osteoarthritis
Radiography
Fractal signature analysis

SUMMARY

Objective: It has been shown that trabecular bone structure parameters extracted from radiographs known as fractal signature analysis (FSA) are able to predict structural outcomes such as radiographic osteoarthritis (OA) progression. Little is known about their involvement in early disease or about differences between subjects exposed to increased joint loading such as young active athletes compared to non-athletes. Aim was to compare horizontal and vertical dimensions of bone texture considering athlete status, gender, previous anterior cruciate ligament (ACL) surgery and age.

Design: Included were 685 patients of which 135 consecutive athletes (82% soccer players) 18–36 years old and 550 non-athletes controls in the same age range had knee radiography for assessment of sub-acute or chronic knee complaints. Regions of interest (ROI) were placed in the subchondral medial and lateral tibial plateaus. Fractal signatures were calculated in the horizontal and vertical dimensions. Curve fitting algorithms were applied taking into account all four risk factors in the same model adjusting for each other.

Results: For the horizontal dimensions significant differences were observed for gender (estimate (E) 0.098 (95% confidence interval(CI)) (−0.009, 0.008), $P < .0001$), previous ACL surgery (E −0.031, 95% CI (−0.043, −0.019), $P < .0001$) and highest age group (E −0.039, 95% CI (−0.048, −0.029), $P < .0001$). For vertical dimensions, significant differences were shown for athletes (E −0.012, 95% CI (−0.020, −0.004), $P < .0001$), gender (E 0.056, 95% CI (0.049, 0.062), $P < .0001$), and age range from 28 to 32 years (E −0.028, 95% CI (−0.037, −0.019), $P < .0001$).

Conclusions: Trabecular bone structure differs between athletes and non-athletes, in regard to previous ACL surgery, gender and higher age.

Introduction

Injury to the knee joint may lead to accelerated joint degeneration in young people, which has been observed especially as long term sequelae of anterior cruciate ligament (ACL) tears[1]. A recent publication on the 5-year outcome of a randomized trial on ACL treatment reported radiographic osteoarthritis (OA) in 12% (tibiofemoral) and 19% (patellofemoral) of participants without differences in the treatment groups[2]. Recently, a study focusing on young active persons reported an increased risk for radiographic OA and osteophyte presence not only for persons with previous ACL surgery but also for high level athletes and higher age[3]. Early peripheral bone changes including osteophytes have been identified as a predictor of radiographic OA incidence[4], but despite these apparent radiographic changes of OA, subchondral bone alterations have been shown to be relevant for OA pathogenesis and progression[5,6].

Lynch and colleagues were the first to analyze bone architecture on radiographs of joints with OA using bone texture or fractal signature analysis (FSA)[7]. The fractal dimension (FD) or signature of cancellous bone takes into account its composite nature, which is determined principally by trabecular number, spacing, and cross connectivity[7,8]. To date most studies investigating bone structure

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http://dx.doi.org/10.1016/j.joca.2015.07.002
1063-4584/

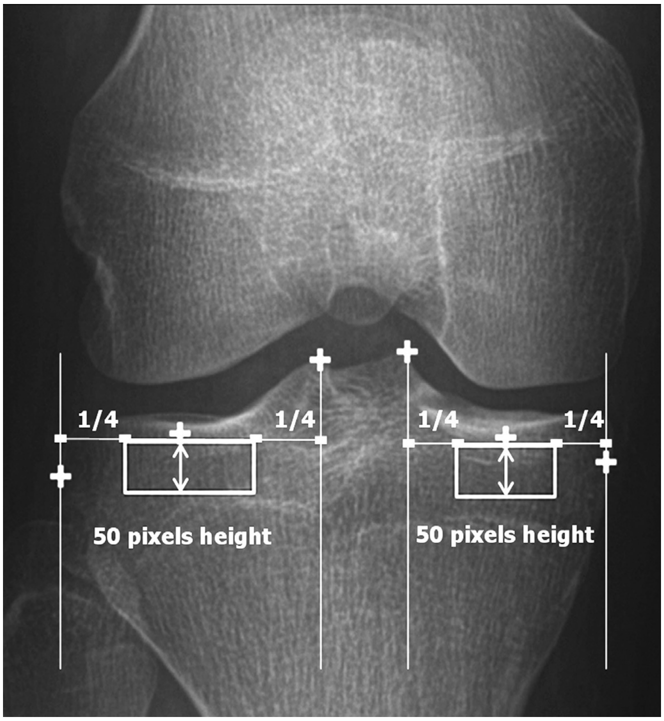

Fig. 1. Example of ROI placement for FSA of the subchondral medial and lateral tibia. The horizontal distance of the ROI was set at the middle two quarters of the distance between the tibial spines and tibial borders (rectangles). The peripheral quarter was excluded to avoid the periarticular osteopenia adjacent to marginal osteophyte formation. Rather than using a predefined horizontal distance, proportional placement at the middle two quarters was applied to take into account the individual variability of the tibial plateau width. A standard vertical distance of 50 pixels (13.23 mm) was applied with the upper horizontal margin directly beneath the subchondral plate.

using FSA have focused on osteoarthritic joints in older subjects and bone texture analysis has been shown to predict radiographic OA progression[6,9].

Little is known about bone texture in young active persons or the very early stages of OA. Only one small study is available that assessed FSA in subjects who had suffered an ACL injury on average 34 months prior and found a significant decrease in FD in the medial compartment with no significant changes in the lateral compartment[10]. Given the repetitive impact of loads to the knee joint in sports like soccer it has to be expected that similarly to adaptations in cartilage also subchondral bone changes as measured by FSA are to be observed[11]. Further it is not known if gender or age has a relevant impact on subchondral bone structure and whether bone texture may potentially serve as a marker to identify athletes and other young persons at increased risk for knee OA.

Thus, the aim of this exploratory analysis was to compare in a cross-sectional fashion horizontal and vertical dimensions of bone texture in a cohort of young active persons considering risk factors of athlete status, gender, previous ACL surgery and age after combining these features into one single model.

Material and methods

Study design and inclusion

The local institutional review board approved the study design and granted exempt status (Anti Doping Lab Qatar, IRB number EX2014000008).

The study was based on a search within the hospital picture archiving and communication system (PACS) system for knee radiography during a 2-year period from January 2011 until December 2012. Based on the referral forms we included consecutive patients between 18 and 36 years of age who presented to an outpatient clinic of a secondary referral center for sports medicine. Patients complained of chronic or subacute pain, but must not have suffered acute knee trauma within the last 4 weeks, as verified by the patients' clinical records. Patients with remote trauma and previous surgery were not excluded. Patients were either walk-ins to the mentioned sports medicine outpatient clinic, referred by a primary care physician or by an orthopaedic surgeon, or were registered athletes under the National Sports Medicine Program (NSMP) of the State of Qatar. The NSMP is a centralized institution that oversees medical diagnosis and treatment of athletes registered in sports clubs in Qatar with the large majority of these being soccer players. All persons who are registered with a sports club in Qatar are under the medical supervision of the NSMP, which was the basis for the definition of an athlete.

Table I
Fractal signature curves for horizontal dimensions including four risk factors adjusting each other*

		Medial compartment		Lateral compartment	
		Estimate (95% confidence intervals)	*P*-value	Estimate (95% confidence intervals)	*P*-value
Athlete status, yes vs no		0.000 (−0.009, 0.008)	0.9614	0.004 (−0.004, 0.011)	0.3359
Gender, Female vs Male		0.098 (0.091, 0.106)	<0.0001	−0.015 (−0.022, −0.008)	<0.0001
Previous ACL surgery, yes vs no		−0.031 (−0.043, −0.019)	<0.0001	−0.058 (−0.069, −0.047)	<0.0001
Age	23–27 vs 18–22	0.048 (0.039, 0.057)	<0.0001	0.005 (−0.003, 0.013)	0.2346
	28–32 vs 18–22	0.004 (−0.006, 0.014)	0.4532	−0.001 (−0.009, 0.008)	0.8857
	32+ vs 18–22	−0.039 (−0.048, −0.029)	<0.0001	−0.040 (−0.049, −0.032)	<0.0001
Radius		−0.004 (−0.006, −0.002)	0.0013	−0.003 (−0.005, −0.001)	0.0038
$Radius^2$		0.168 (0.168, 0.169)	<0.0001	0.155 (0.154, 0.155)	<0.0001
Athlete × Radius		0.000 (−0.002, 0.003)	0.7467	0.002 (0.000, 0.004)	0.1185
Athlete × $Radius^2$		0.000 (−0.001, 0.001)	0.7076	−0.001 (−0.001, 0.000)	0.0837
Gender × Radius		−0.003 (−0.005, 0.000)	0.0421	−0.001 (−0.003, 0.001)	0.3245
Gender × $Radius^2$		−0.012 (−0.013, −0.011)	<0.0001	0.002 (0.001, 0.002)	<0.0001
ACLR × Radius		0.001 (−0.002, 0.004)	0.5720	0.000 (−0.003, 0.003)	0.7947
ACLR × $Radius^2$		0.004 (0.002, 0.005)	<0.0001	0.007 (0.006, 0.007)	<0.0001
Agecat (23–27) × Radius		−0.001 (−0.004, 0.002)	0.3885	0.000 (−0.003, 0.002)	0.8309
Agecat (28–32) × Radius		−0.001 (−0.003, 0.002)	0.7438	−0.001 (−0.003, 0.002)	0.6551
Agecat (32+) × Radius		−0.001 (−0.004, 0.002)	0.4276	−0.001 (−0.003, 0.002)	0.6796
Agecat (23–27) × $Radius^2$		−0.006 (−0.007, −0.005)	<0.0001	−0.001 (−0.001, 0.000)	0.2139
Agecat (28–32) × $Radius^2$		−0.001 (−0.001, 0.000)	0.3498	0.000 (−0.001, 0.001)	0.8253
Agecat (32+) × $Radius^2$		0.005 (0.004, 0.006)	<0.0001	0.004 (0.004, 0.005)	<0.0001

* Parameter estimates are determined by mixed effect model testing taking into account all risk factors.

Table II
Fractal signature curves for vertical dimensions including four risk factors adjusting each other*

		Medial compartment		Lateral compartment	
		Estimate (95% confidence intervals)	*P*-value	Estimate (95% confidence intervals)	*P*-value
Athlete, yes vs no		−0.012 (−0.020, −0.004)	0.0047	−0.021 (−0.029, −0.013)	<0.0001
Gender, F vs M		0.056 (0.049, 0.062)	<0.0001	0.053 (0.047, 0.060)	<0.0001
ACLR, yes vs no		−0.005 (−0.015, 0.005)	0.3420	−0.018 (−0.029, −0.007)	0.0009
Age	23–27 vs 18–22	0.002 (−0.006, 0.011)	0.6102	0.018 (0.009, 0.026)	<0.0001
	28–32 vs 18–22	−0.028 (−0.037, −0.019)	<0.0001	0.004 (−0.005, 0.013)	0.3773
	32+ vs 18–22	0.008 (−0.001, 0.016)	0.0864	0.000 (−0.008, 0.008)	0.9857
Radius		−0.005 (−0.007, −0.003)	<0.0001	−0.004 (−0.006, −0.003)	<0.0001
Radius^2		0.176 (0.175, 0.176)	<0.0001	0.175 (0.174, 0.175)	<0.0001
Athlete × Radius		−0.001 (−0.003, 0.001)	0.4210	0.002 (0.000, 0.004)	0.0224
Athlete × Radius^2		0.002 (0.001, 0.002)	0.0001	0.002 (0.002, 0.003)	<0.0001
Gender × Radius		−0.003 (−0.005, −0.001)	0.0002	−0.003 (−0.004, −0.001)	0.0012
Gender × Radius^2		−0.006 (−0.007, −0.005)	<0.0001	−0.006 (−0.006, −0.005)	<0.0001
ACLR × Radius		−0.001 (−0.003, 0.002)	0.6282	0.003 (0.001, 0.006)	0.0069
ACLR × Radius^2		0.001 (0.000, 0.002)	0.1961	0.002 (0.001, 0.003)	0.0004
Agecat (23–27) × Radius		0.002 (0.000, 0.004)	0.1244	−0.003 (−0.004, −0.001)	0.0125
Agecat (28–32) × Radius		0.005 (0.003, 0.007)	<0.0001	0.001 (−0.001, 0.003)	0.4939
Agecat (32+) × Radius		0.001 (−0.001, 0.003)	0.4071	0.000 (−0.002, 0.002)	0.7823
Agecat (23–27) × Radius^2		0.000 (−0.001, 0.000)	0.5225	−0.002 (−0.002, −0.001)	<0.0001
Agecat (28–32) × Radius^2		0.003 (0.002, 0.003)	<0.0001	0.000 (−0.001, 0.000)	0.2754
Agecat (32+) × Radius^2		−0.001 (−0.002, 0.000)	0.0415	0.000 (−0.001, 0.001)	0.8814

*Parameter estimates are determined by mixed effect model testing taking into account all risk factors.

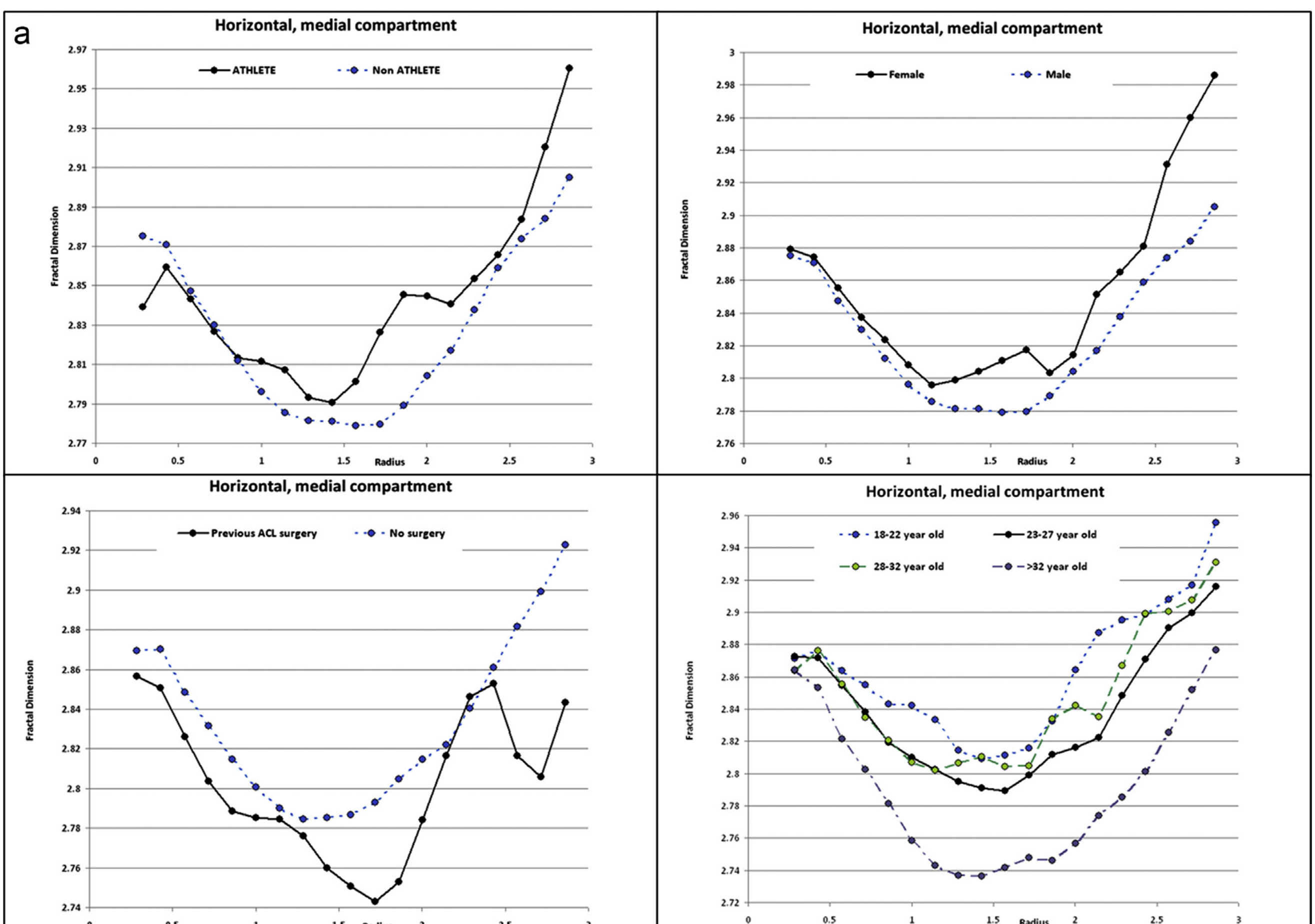

Fig. 2. (a). Comparison of FSA curves from patients with or without specific risk factors. Figure part displays results for the horizontal component for the medial tibia. Each curve represents the 19 different radii (X-axis) and the FDs in the Y-axis. Curve fittings exhibit lower mean FDs in the horizontal component in non-athletes, males, patients with previous ACL surgery and increasing age. (b). For the lateral compartment curves fittings exhibit lower mean FDs in the horizontal component for non-athletes, females, patients with previous ACL surgery and increasing age. (c). For the medial compartment and the vertical component curves fittings exhibit lower mean FDs for athletes, males, patients with previous ACL surgery and only minor differences for increasing age. (d). For the lateral compartment and the vertical component curves fittings exhibit lower mean FDs for athletes and males. Only minimal differences were observed for patients with previous ACL surgery and different age groups.

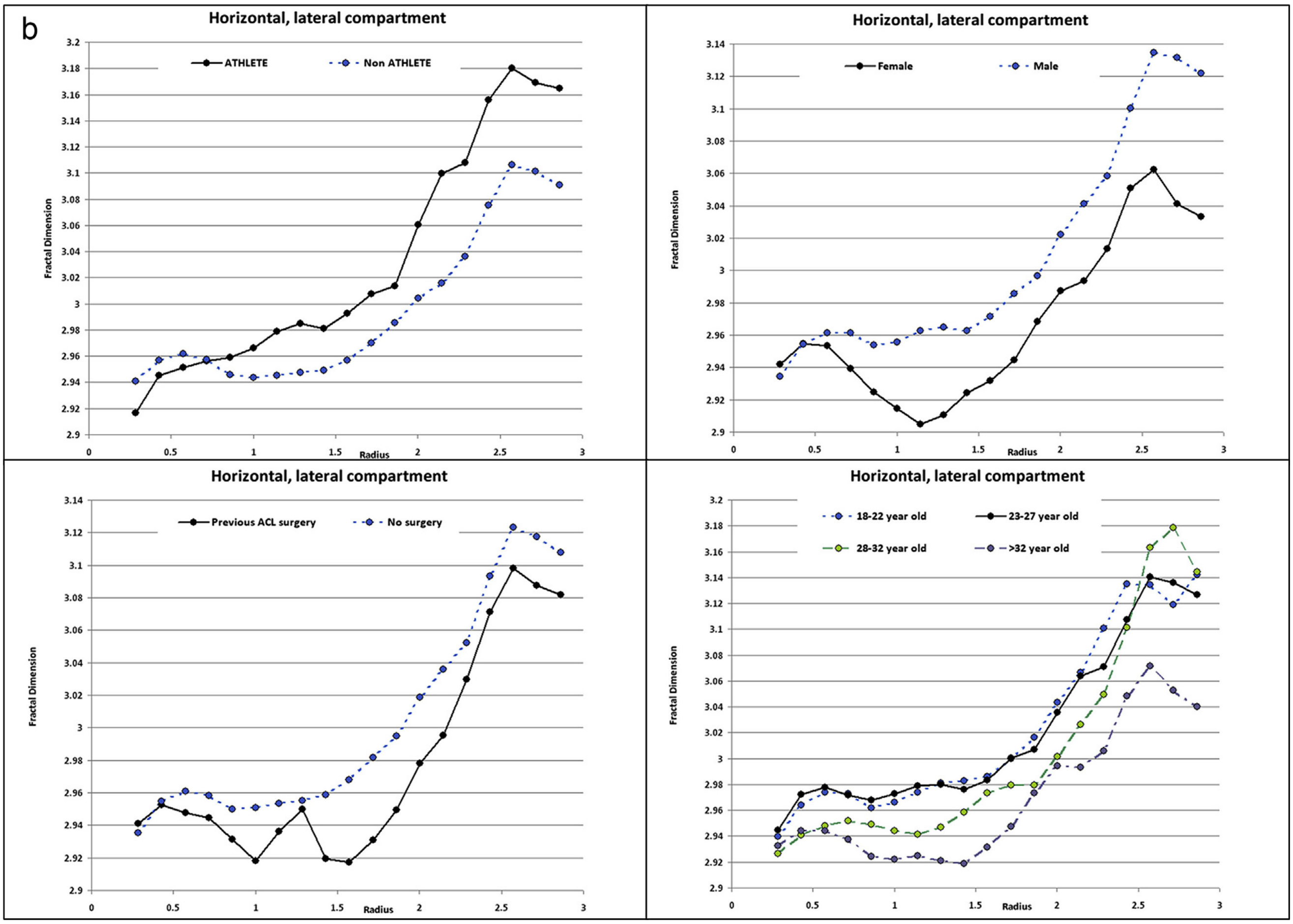

Fig. 2. (*continued*).

We included information on previous ACL surgery as diagnosed by hardware on the radiographs, but did not have a chance to extract data on other types of surgery. Within our PACS search approach we only took into account either bilateral (of which only the right knee was included and analyzed) or single view right knees.

Radiography

A posteroanterior (PA) view of the knee was acquired with the Lyon-Schuss fluoroscopy protocol. Images were acquired in digital fashion with a standard clinical fluoroscopy system and a film-focus distance of 180 cm. Radiographic assessment was performed according to the Kellgren–Lawrence system with results having been presented previously[3]. Only the right knees of patients were included whenever there were bilateral radiographs available ($n = 464$, 67.7%). The remainder of the patients had single view right knees that were available for analysis.

All radiographic images were reviewed by a musculoskeletal radiologist (MJ) for quality assurance, which was based on ideal visualization of the medial tibiofemoral joint space. Whenever the medial joint space was visualized in a suboptimal fashion the knee was excluded. Altogether 8% of the knees ($n = 60$) were excluded from the study due to insufficient image quality.

Bone texture analysis

Pre-defined regions of interest (ROI) were placed in the subchondral medial and lateral tibial plateaus, immediately under the cortical plates. The landmarks used were the medial and lateral tibial borders, medial and lateral tibial spines, and the medial and lateral subchondral plates. Figure 1 shows a representative example of region of interest (ROI) placement in the subchondral areas of the medial and lateral tibial plateaus. The horizontal distance of the ROI was placed in the middle two quarters of the distance between the tibial spine and tibial border. The peripheral quarter was excluded to avoid the periarticular osteopenia adjacent to marginal osteophyte formation, similarly to previous studies[9]. Proportional placement at the middle two quarters was chosen to take into account the individual variability of the tibial plateau width. A standardized vertical distance of 50 pixels (13.23 mm) was selected. Knees with ACL hardware or tunnel, or fibular head overlapping the ROI were excluded. No manual adjustment was performed. Image resolution was 0.05 mm × 0.05 mm. FSA were calculated in the horizontal and vertical dimensions according to the method by Buckland-Wright *et al.*[8]. 19 trabecular image sizes (radii) were applied ranging from 0.9 mm to 2.9 mm.

Analytic approach

Patients were stratified into athletes and non-athletes (according to status of registration with the NSMP), and additional stratification was performed according to gender, ACL surgery status, and age. We used linear mixed effect model to assess whether bone texture on the horizontal dimension was associated with the four risk factors, athletes (yes vs no), gender (female vs male), ACL surgery (yes vs no), and age (23–27, 28–32, 32+ vs 18–22 years),

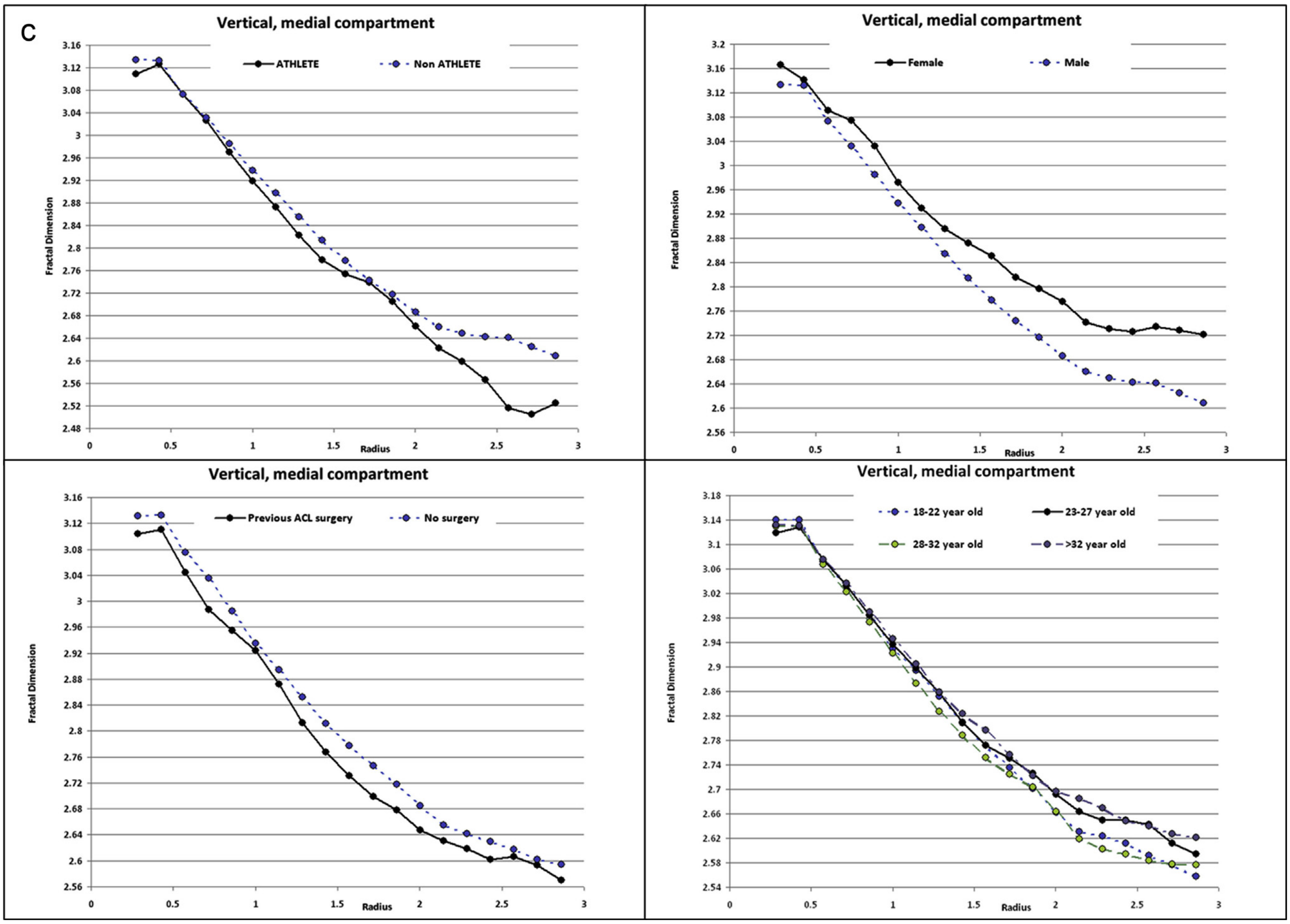

Fig. 2. (*continued*).

adjusting for each other and the shape of polynomial curves of the bone texture on radii[6]. Participant nested in the exposure levels was included as a random factor variable to account for inter-individual variation (random intercept). The risk factors were included as fixed categorical explanatory variables. We used the same approach to assess the association between the four risk factors and bone texture on the vertical dimension.

Results

Included were 685 patients of which 135 were athletes. In regard to sports played, the majority ($n = 110$, 81%) of athletes were soccer players, which was coded in the referral forms. However, an additional breakdown in different sports types was not possible. 556 (81.2%) were male and 60 (8.8%) patients had previous ACL surgery. The ethnic background of the patients was not coded but most patients were of Middle Eastern ethnic origin.133 (19.4%) patients were in the age group 18–22 years, 181 (26.4%) in the range of 23–27, 155 (22.6%) in the range of 28–32 and 216 (31.5%) were between 33 and 36 years old. Mean age was 28.5 years (SD $\pm$ 6.5) and 8.5% had tibiofemoral OA defined as Kellgren–Lawrence grade two or more.

A detailed overview of the results for the horizontal and vertical FDs for the medial and lateral tibial plateaus is presented in Tables I and II. In summary, for the horizontal dimensions significant differences were observed for gender (estimate (E) 0.098, (95% confidence interval(CI)) (−0.009, 0.008), $P < .0001$), previous ACL surgery (E −0.031, 95% CI (−0.043, −0.019), $P < .0001$) and the highest age group (E −0.039, 95% CI (−0.048, −0.029), $P < .0001$). For vertical dimensions, significant differences were shown for athletes (E −0.012, 95% CI (−0.020, −0.004), $P < .0001$), gender (E 0.056, 95% CI (0.049, 0.062), $P < .0001$), and age range from 28 to 32 years (E −0.028, 95% CI (−0.037, −0.019), $P < .0001$). Figure 2 displays the FSA curves over all 19 dimensions in the multi-adjusted model for the different features, i.e., athlete status, gender, previous ACL surgery and the different age categories. In brief, FDs calculated for athletes' horizontal trabeculae were significantly higher than non-athletes. Lower FDs were observed for those calculated from vertical trabeculae, medially and laterally. For female gender, FDs were lower for horizontal trabeculae medially but higher laterally. For vertical trabeculae, males had lower FDs than females. Subjects with previous ACL surgery had lower FDs for medial and lateral compartments and horizontal and vertical trabeculae. Finally, higher age resulted in lower FDs compared to the lowest age group especially for horizontal trabeculae with overall age showing non-uniform results.

Discussion

We found significant differences in trabecular bone structure between athletes and non-athletes, in regard to previous ACL surgery, for gender and for higher age. Specific differences observed for the horizontal and vertical dimensions of FSA warrant further exploration since they are not easily interpreted.

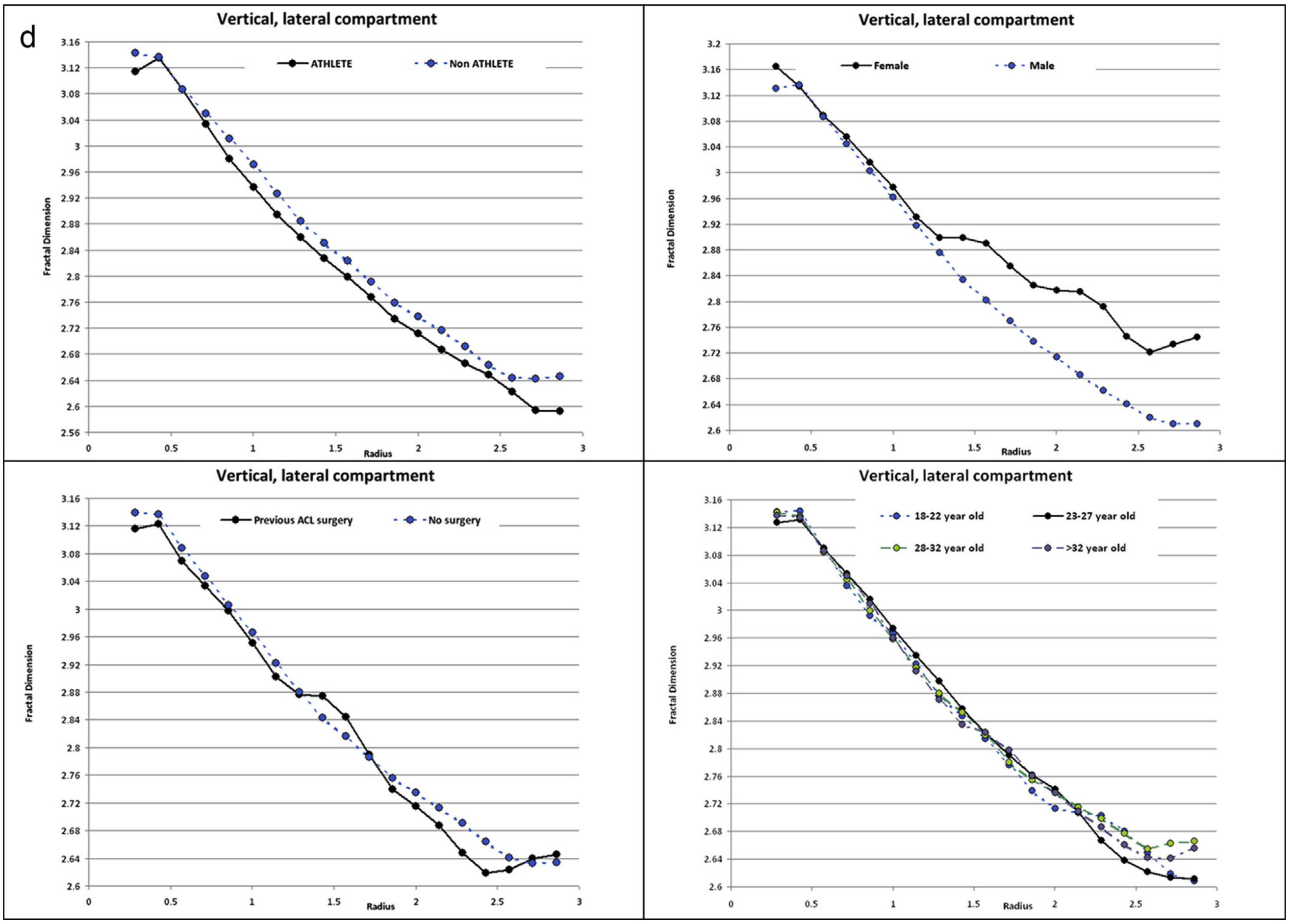

Fig. 2. (*continued*).

FSA is a potentially valuable analytic tool for characterizing the complicated histomorphometry of bone[12]. Several analytic approaches have been described and data is difficult to compare across different studies[6,9,13]. To achieve a more global picture of trabecular changes we used a curve fitting approach similarly to the one described by Kraus *et al.* who found that higher fractal signatures of vertical trabeculae and lower fractal signatures of horizontal trabeculae at baseline were able to distinguish OA progressors from non-progressors[6]. In contrast, Podsiadlo and colleagues described lower FDs for OA subjects that had undergone medial meniscectomy for horizontal and vertical dimensions[9]. Our study population is not easily comparable with these studies as it was comprised of young active persons with only a minority having radiographic OA. We have recently published results on the same cohort describing frequencies of OA radiographic features for the same subgroups and found that athlete status, higher age and previous ACL surgery increase the risk of radiographic OA with surgery being the strongest risk factor[3]. Our FSA data add to these observations in that we observed significant differences for FSA parameters in both compartments and in both, the horizontal and vertical dimensions. Especially for previous surgery we found lower FDs in both tibiofemoral compartments for both, vertical and horizontal trabeculae suggesting early subchondral bone alterations due to altered biomechanics. The decrease in the fractal signature for the horizontal structures that we observed is consistent with an increase in trabecular thickness and has also been described by Buckland-Wright *et al.* in their cohort of ACL injured patients[10]. However, while this study did not find significant changes in the lateral tibia, we did see differences especially for gender, previous ACL surgery and highest age group also in the lateral compartment which reflects the patient population analyzed and potentially due to the higher number of subjects in or study.

Other studies have described differences between OA and non-OA knees applying different analytic approaches such as augmented Hurst orientation transform or a variance orientation transform method[9,13]. To date no standardization of the different methods has been achieved and further work is needed to compare these different methodologies.

Recent studies showed that OA changes occur primarily in trabeculae ranging in sizes from 0.12 to 1.14 mm[14]. Based on this finding, the high resolution provided by modern digital radiographic acquisition methods as used in this study is adequate to cover this spectrum. As is true for semi-quantitative or quantitative assessment, positioning of the knee joint plays an important role also for FSA. Using a positioning frame or a standardized fluoroscopic protocol as we have used these challenges may be overcome[15].

As a shortcoming we have to acknowledge that the study population was heterogeneous and based on a retrospective search with patients presenting with a spectrum of clinical complaints. As imaging was performed for a clinical reason, our study population is certainly not representative of the general population in this age group. Our study population had a mixed ethnic background with a majority being of Middle East origin. Whether bone structure parameters differ between subjects of different ethnic or geographic origin needs to be further explored. Patient inclusion was based on the status of being a registered athlete with the large majority of patients being soccer players. We further have to acknowledge that non-registered patients might have been allocated to the non-athlete group but based on their physical activity level should rather be considered “athletes” than “non-athletes”. Unfortunately, we did not have the possibility to identify these patients based on the information available. The information of duration since registration as an athlete with the NSMP was not available.

In summary, we found significant differences for all parameters analyzed. However, additional work is warranted to standardize the different methods that are applied to be able to compare data across different study populations. FSA appears to be a promising tool to define early subchondral bone alterations in young active subjects.

Authors contributions

(1) All authors were involved in the conception and design of the study, or acquisition of data, or analysis and interpretation of data.
(2) All authors contributed to drafting the article or revising it critically for important intellectual content.
(3) All authors gave their final approval of the manuscript to be submitted.

Additional contributions

- Analysis and interpretation of the data: FWR; MJ; JN; JD; JAL; AG.
- Drafting of the article: FWR; MJ; JN; JD; JAL; AG.
- Provision of study materials or patients: FWR, AG.
- Statistical expertise: JN.
- Obtaining of funding: FWR, AG.
- Collection and assembly of data: FWR; AG; MJ; JD.

Responsibility for the integrity of the work as a whole, from inception to finished article, is taken by F. Roemer, MD (first author; frank.roemer@aspetar.com).

Funding and role of the funding source

The study was funded by ASPETAR.

Conflict of interests

Dr Guermazi has received consultancies, speaking fees, and/or honoraria from Sanofi-Aventis, Merck Serono, and TissuGene and is President and shareholder of Boston Imaging Core Lab (BICL), LLC a company providing image assessment services. Dr Roemer is Chief Medical Officer and shareholder of BICL, LLC. None of the other authors have declared any competing interests.

Acknowledgments

We wish to thank all staff members of the Department of Radiology at ASPETAR.

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